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(54) Title: SUSTAINED RELEASE FORMULATION CONTAINING THREE DIFFERENT TYPES OF POLYMERS

(57) Abstract

Verapamil depot drug formulations include the pharmaceutical itself and a three component release rate controlling matrix composition. The three components of the matrix composition are (1) an alginate component, such as sodium alginate, (2) an enteric polymer component, such as methacrylic acid copolymer, and (3) a pH independent gelling polymer, such as hydroxypropyl methylcellulose or polyethyleneoxide. The drug release rate can be adjusted by changing the amount of one or more of these components of the composition.

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SUSTAINED RELEASE FORMULATION CONTAINING THREE DIFFERENT TYPES OF POLYMERS

Field of The Invention

The present invention is directed to formulations for preparing sustained release drug forms useful for releasing pharmaceuticals at controlled rates, generally in the stomachs and/or gastrointestinal tracts of hosts. In particular the invention relates to an improved depot drug form useful in connection with preparing sustained release tablets.

Background of the Invention

A zero order release profile for a drug from its controlled release dosage form sometimes is desirable in clinical use. The technology used to formulate zero order release dosage forms is well documented. The entrapment of a drug in a matrix is a common approach to formulate sustained release tablets with a zero order release profile.

It has been reported that depot drug formulations for controlled release of pharmaceutical drugs may be prepared using alginates alone (see U.S. patent no. 5,132,295), using combinations of alginates and polyacrylates (see U.S. patent no. 5,230,901) and using combinations of alginates and a pH independent hydrocarbon gelling agent, such as, for example, hydroxypropylmethyl cellulose (se U.S. patent no. 4,792,452). It is also known that the use of alginates alone for this purpose often presents difficulties in

tableting, film coating and storage.

Adding polyacrylates to the alginate formulation overcomes these difficulties to some extent; however, tablets formed using alginates and polyacrylates often have a pH dependent dissolution profile. In a low pH environment, alginates and polyacrylates do not swell and/or dissolve properly. This leads to drug release by a diffusion mechanism through non-viscous capillaries resulting in a different dissolution rate than in a high pH environment. On the other hand, in a high pH environment, alginates swell and become soluble while polyacrylates may or may not do the same. This leads to drug release both by erosion and diffusion at a rate which is different than the low pH release rate.

In formulations which include an alginate and a pH independent gelling polymer such as, for example, hydroxypropylmethyl cellulose, such polymers hydrate at low pH levels to create a viscous gel layer for drug release. At high pH levels, however, tablets become smaller and smaller during drug release due to polymer erosion, and this leads to a reduction in surface area which may affect dissolution rate.

The novelty of the present invention is the provision of a sustained release formulation which reduces, and perhaps eliminates these problems completely. In particular the invention provides a controlled release drug formulation which includes an alginate compound, an enteric polymer, such as polyacrylate, and a gelling

polymer, such as, for example, hydroxypropylmethyl cellulose. Such a combination of ingredients facilitates manufacturing procedures and improves drug dissolution profile.

In the formulation in accordance with the present invention, the gelling polymer provides excellent binding and controlled release characteristics thereby facilitating the manufacturing processes. During dissolution, hyroxypropyl methylcellulose hydrates to form a gel layer to control drug release at low pH levels. At high pH levels, enteric polymer increases erosion rate so as to maintain a constant dissolution rate regardless of tablet size. So reduction in tablet size does not reduce release rate. Thus, the formulations of the present invention provide improved drug release profiles compared with the prior art formulations described above.

Detailed Description of the Preferred Embodiments

The present invention provides sustained release tablets formulated with a mixture of a pharmaceutical composition, an alginate, an enteric polymer and a pH independent gelling polymer from which the pharmaceutical composition may be released at a controlled rate. In a particularly preferred form of the invention, the formulation may be used to provide a depot drug form for controlled release of a verapamil containing pharmaceutical composition. However, the formulation is also useful in connection with a variety of other pharmaceutical compositions and the

invention should not be considered as being limited by the exact composition and/or nature of the pharmaceutical composition which is released under controlled conditions therefrom.

In a preferred form, the formulation of the invention may contain 1) an alginate component in the form of a water soluble salt of an alginic acid having a viscosity within the range of from about 60 to about 10,000 centipoises, and preferably from about 100 to about 6,000 centipoises, in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer; 2) An enteric polymer composition component, such as a cellulose derivative or a methacrylic acid copolymer (preferably ®Eudragit L/S); and 3) a pH independent gelling polymer component, such as a cellulose derivative or polyethyleneoxide, having a viscosity within the range of from about 10 to about 100,000 centipoises, and preferably from about 50 to about 15,000 centipoises in a 2% by weight water solution at 20° C.

The overall tablet formulation should include the alginate component in an amount so as to establish a weight ratio of alginate:active drug of from about 0.5:1 to about 3:1, and preferably from about 0.7:1 to 1.5:1, in the formulation. Furthermore, the overall tablet formulation should also include the enteric polymer, such as polyacrylate composition component in an amount so as to establish a weight ratio of enteric polymer:active drug of from about 0.1:1 to about 2:1, and preferably from about

0.2:1 to 1:1, in the formulation. Still further, the overall tablet formulation should also include the pH independent gelling polymer component in an amount so as to establish a weight ratio of gelling polymer:active drug of from about 0.03:1 to about 2:1, and preferably from about 0.1:1 to 1:1, in the formulation.

Suitable enteric polyacrylate materials are fully described, for example, in U.S. letters patent no. 5,230,901, the entirety of the disclosure of which is incorporated herein by reference. In this regard, the term polyacrylate is used herein to encompass the polyacrylates, the polymethacrylates and the copolymers of acrylic and methacrylic acid disclosed in the '901 patent. These materials are also described in, for example, Houben-Weyl, Methoden der organischen Chemie, Thieme-Verlag, Stutt, 1961. Products which are commercially available under the name Eudragit® are particularly suitable. Other suitable enteric polymers include, for example, cellulose derivatives such as, cellulose acetate phthalate, cellulose phthalate hydroxypropylmethyl ether, polyvinyl acetate phthalate, etc.

Other ingredients which may be optionally included in the formulation of the invention include 1) one or more binders such as, for example, povidone (polyvinylpyrrolidone), modified starch, low viscosity hydroxypropylmethyl cellulose, etc.; 2) one or more fillers such as, for example, microcrystalline cellulose, lactose, starch, calcium sulfate, etc.; 3) one or more lubricants such as,

for example, magnesium stearate, stearic acid, etc.; 4) one or more coating film formers such as, for example, Opadry (a hydroxypropylmethyl cellulose based coating system); and 5) one or more colorants such as, for example, FD&C green dye. The binder materials may be present in an amount up to about 10% by weight of the entire formulation and the lubricant materials may be present in an amount within the range of from about 0.1% to about 5.0% by weight of the entire formulation.

In the specific examples set forth below, three specific embodiments of the invention are exemplified. Theses embodiments have been designated A, B and C.

SPECIFIC EXAMPLES OF THE PREFERRED EMBODIMENTS

COMPONENT	AMOUNT OF COMPONENT IN EACH EMBODIMENT		
	A	B	C
1. VERAPAMIL HCL	240 MG	120 MG	240 MG
2. SODIUM ALGINATE	250 MG	80 MG	200 MG
3. HYDROXYPROPYLMETHYL CELLULOSE	50 MG	15 MG	--
4. POLYETHYLENEOXIDE	--	--	60 MG
5. METHACRYLIC ACID COPOLYMER (®Eudragit L/S)	120 MG	30 MG	100 MG
6. POVIDONE	50 MG	25 MG	40 MG
7. MICROCRYSTALLINE CELLULOSE	60 MG	80 MG	80 MG
8. MAGNESIUM STEARATE	5 MG	2 MG	5 MG

Items 1 through 7 listed above are mixed in a mixer such as a high shear mixer granulator or planetary mixer to obtain homogeneity. The mix is then granulated in water or other suitable granulation fluids and dried in a dryer. The dried granular mass is then milled and then item 8 (a lubricant) is added during milling. The lubricated granular mass is then compressed into tablets using a tablet press. The foregoing steps are conventional steps used in the tablet forming industry.

In the preferred embodiments set forth above, the formulations of the invention have particular utility in the preparation of sustained release tablets of verapamil. However, the invention is not limited to use in connection with this drug only. Tablets containing other drugs requiring sustained release are as well within the intended scope of the invention. For example, it is contemplated that the sustained release formulations of the invention have utility in connection with drugs such as propafenone, barucainide, nesapidil, gallopamil and biperiden. Other suitable pharmaceutical drugs which may require sustained release and which therefore are within the scope of the present invention are listed in U.S. patent no. 4,792,452 to Howard et al., the entirety of the disclosure of which is hereby specifically incorporated by reference.

WE CLAIM:

1. A tablet for sustained release of a drug comprising an effective amount of a drug to be released over a period of time; an alginate compound; an enteric polymer; and a pH independent gelling polymer.

2. A tablet for sustained release of a drug comprising an effective amount of a drug to be released over a period of time; an alginate component; an amount of an enteric polymer effective at high pH levels to improve release rate due to tablet size change in the dissolution process; and an amount of a pH independent gelling polymer effective to promote binding and controlled release in the tablet.

3. A tablet as set forth in claim 2, wherein said gelling polymer comprises hydroxypropylmethyl cellulose.

4. A tablet as set forth in claim 2, wherein said enteric polymer comprises a methacrylic acid copolymer.

5. A tablet as set forth in claim 2, wherein said enteric polymer comprises a cellulose derivative.

6. A tablet as set forth in claim 2, where said alginate

component is a water soluble salt of alginic acid having a viscosity within the range of from about 60 to about 10,000 centipoises in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer.

7. A tablet as set forth in claim 6, where said alginate component is a water soluble salt of alginic acid having a viscosity within the range of from about 100 to about 6,000 centipoises in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer.

8. A tablet as set forth in claim 2, wherein said pH independent gelling polymer component is a cellulose derivative.

9. A tablet as set forth in claim 2, wherein said pH independent gelling polymer component is polyethyleneoxide.

10. A tablet as set forth in claim 2, wherein said pH independent gelling polymer component has a viscosity within the range of from about 10 to about 100,000 centipoises in a 2% by weight water solution at 20° C.

11. A tablet as set forth in claim 10, wherein said pH independent gelling polymer component has a viscosity within the

range of from about 50 to about 15,000 centipoises in a 2% by weight water solution at 20° C.

12. A controlled release formulation for use in forming a depot drug form in conjunction with a pharmaceutical compound comprising an alginate component, an amount of an enteric polymer effective at high pH levels to improve dissolution rate due to tablet size change in the dissolution process, and an amount of a pH independent gelling polymer effective to promote binding and controlled release in the tablet.

13. A controlled release formulation as set forth in claim 12 comprising a pharmaceutical active drug; an amount of said alginate component ranging from 0.5:1 to 3:1 based on the ratio of the said alginate to active drug; an amount of said enteric polymer ranging from 0.1:1 to 2:1 based on the ratio of the said enteric polymer to active drug; and an amount of said pH independent gelling polymer ranging from 0.03:1 to 2:1 based on the ratio of said pH independent gelling polymer to active drug.

14. A controlled release formulation as set forth in claim 13 wherein said alginate component is a water soluble salt of an alginic acid having a viscosity within the range of from about 60 to about 10,000 centipoises in a 2% by weight water solution at 25°

C, as measured by a Brookfield LV viscometer and said pH independent gelling polymer component has a viscosity within the range of from about 10 to about 100,000 centipoises in a 2% by weight water solution at 20° C.

15. A controlled release formulation as set forth in claim 14 comprising 240 parts by weight verapamil as said pharmaceutical compound, 250 parts by weight sodium alginate as said alginate component, 50 parts by weight hydroxypropylmethyl cellulose as said gelling polymer, 30 parts by weight methacrylic acid copolymer as said enteric polyacrylate, 50 parts by weight polyvinylpyrrolidone, 60 parts by weight microcrystalline cellulose, and 5 parts by weight magnesium stearate.

16. A controlled release formulation as set forth in claim 13 comprising 120 parts by weight verapamil as said pharmaceutical compound, 80 parts by weight sodium alginate as said alginate component, 15 parts by weight hydroxypropylmethyl cellulose as said gelling polymer, 120 parts by weight methacrylic acid copolymer as said enteric polyacrylate, 25 parts by weight polyvinylpyrrolidone, 80 parts by weight microcrystalline cellulose, and 2 parts by weight magnesium stearate.

17. A controlled release formulation as set forth in claim 13

comprising 240 parts by weight verapamil as said pharmaceutical compound, 200 parts by weight sodium alginate as said alginate component, 60 parts by weight polyethyleneoxide as said gelling polymer, 100 parts by weight methacrylic acid copolymer as said enteric polyacrylate, 40 parts by weight polyvinylpyrrolidone, 80 parts by weight microcrystalline cellulose, and 5 parts by weight magnesium stearate.

18. A controlled release formulation as set forth in claim 13 wherein said active drug is verapamil.

19. A controlled release formulation as set forth in claim 13 wherein said amount of said alginate component ranges from 0.7:1 to 1:1.

20. A controlled release formulation as set forth in claim 13 wherein said amount of said enteric polymer ranges from 0.2:1 to 1:1.

21. A controlled release formulation as set forth in claim 13 wherein said amount of said gelling polymer ranges from 0.1:1 to 1:1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/01711

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/22
US CL :424/464, 465, 468, 486, 487, 488
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 465, 468, 486, 487, 488

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,708,874 A (P. DE HAAN ET AL.) 24 November 1987, column 3, lines 22-35 and 55-63, column 4 lines 11-36.	1-5, 8 and 12
X	US 5,128,142 A (S. MULLIGAN ET AL.) 07 July 1992, column 3, lines 30-68, example 17, claims 1-3.	1-5, 8 and 12
X	US 5,230,901 A (H. EINIG ET AL.) 27 July 1993, examples 1-4.	1, 2, 4, 8 and 12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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